



اللجنة العلمية لكلية الصيدلة الدفعة الثانية

ملخص مادة كيمياء دوائية محاضره 9 و 10
عمل طلاب المجموعه المجموعه ال6 سادسة 6



الباراسيتامول - دقة افعاله - متوجه على اعضاء معينة (مثلا الدماغ ...)
 السيتاوي - دقة عمل - متوجه على اعضاء معينة (مثلا قلب ...)

نحوه وجود تحكم كبير للسيتاوي على القلب لهذا لا يعني ان الباراسيتامول موجود دائما ووجوده قليل جدا في قلبه زودنا جرعة سيتاوي لكن اكتبتم بكل رئيسي في القلب و
 السيتاوي

والوظيفة خاصة :- لا يمكن ارفع استجابات ابارا فعال (مثلا لا يمكن رفع ضربات القلب وبارا اكثر)
 وبالتالي para-antagonist ← Sympathetic-agonist

فيكون مع Sympathetic-agonist كأنها Para-antagonist
 ويكون مع Sympathetic-antagonist كأنها Para-agonist

كل عضو في جسم مع Sympathetic و Parasympathetic
 المستقلات فوق ال Sympathetic مهم تعرفها بالتفصيل (كل مستقبل اين يقع)
 امام مستقبلات الباراسيتامول M₁ في القلب ← M₂ و M₃ في بقية اجزاء الجسم من غير تحديد لانه لا يوجد دواء في السوق Selective على M₂ فقط او M₁ فقط
 بالإضافة الى اننا لما نتكلم على ادوية Para نتكلم على Action اكثر من كلامنا على المستقبل.

وظيفة ادوية Para هو جعل كل Sympathetic
 اكثر افعالية في الصيد لان ادوية para-antagonist يعني Sympathetic
 الجهاز السيتاوي والجوارسيتاوي دائما في حالة توازن اذا قل التوازن قد يكون بداية ضغط
 او اي مشاكل صحية اخرى (بما ان اسباب الضغط عدم التوازن لان السيتاوي او الباراسيتاوي)

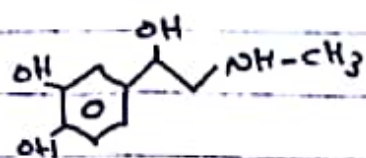
منع السيتاوي ← Thoracic و lumbar

منع الجوارسيتاوي ← X و X و X و X
 ↓ ↓ ↓ ↓
 ١ ٢ ٣ ٤

Acetylcholine يتكسر الى

معنا

استايل كولين

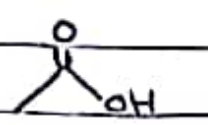


ادريناليين



الاستايل كولين هو ناتج تفاعل الادريناليين و السورادريناليين اليه خلق للاستايل كولين مستقبل خاص و الادريناليين مستقبل خاص فيه وبالتالي مستقبل اي ناقل يدخل كذا (ثاني)

الاستايل كولين له اجبي انزيم اسمه **Esterase** (مادام هو **esterase** يعني يكسر الاستر والاستر يعني تفاعل كيميائي **hydrolysis** يعني يضيف ماء



حمض خليك

acetic acid



كولين



Esterase



acetyl or acetyl

(الاولي بعد تخزينه مناجيد لان مصدره نادره)

اما الادريناليين يتأكسد بال **MAO** وال **COMT** (MAO - MAO - MAO) يعيد اكد الى حمض وال **COMT** - **O-Methyl** وخرجه (كان الادريناليين و السورادريناليين مصدرهم متوفر بكثرة - اصبحت الاستايل كولين مصدرة نادرة و كان هذا يتم تخزينه

الاستايل كولين لو قل يعمل زفير ولكن لو زاد يعمل **Parkinsonism**

كلما كبر الانسان بالعمر يقل تركيز مستقبلات الاستايل كولين

الادوية التي تؤثر على ال **Parasympathetic** (cholinergic) **anticholinergic**

Direct

Indirect

نروح نجيب انزيم مشابه للمستقبل

mimetic او

agonist او

cholinergic

نروح نجيب انزيم يكسر الاستايل كولين

الذي يكسر الاستايل كولين



Anti-cholinergic

Anti muscarinic

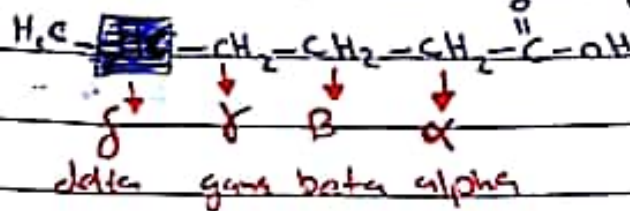
Neuromuscular
blocker

Ganglion
blocker

(ماریتو هست)

الاینتیل کولین استریز سے دیکس اینتیل کولین
*** Sympathetic زیادہ اور parasympathetic کم

آئی ٹی ڈیزائن



نیم حالت کانت β یعنی Muscarinic اکثریت
اما اذا كانت جينار α فهي تفاعل M اکثریت

سؤال هست اصروف Parasympathetic-agonist

۱- في حالة Glucagon - ينقص الضغط 10P - miosis
۲- في حالة phosostigmine او physostigmine (توسيع) (اول ما تشرف) (توسيع)
نقول تقريباً وهن العضلات

~~3- في حالة atropine - يزيد الضغط 10P - mydriasis~~

۴- يعالج الزلزال

۵- يرفع الضغط - لان ادوية التخدير تخفض الضغط

*** ولا دخل اذا اردنا ان نرفع الضغط فقط Sympathetic-antagonist

Day / /

٥

الاستجابة كولين متر موجود بالسوق لعدة اسباب

(١) قصير المدى (short duration)

(2) ester (3) متحون (4) nonselective تفال على كل شيء M

ولذلك امتصاصه ضعيف

اذا لم يكن موجود بالسوق وانما يوجد فقط الطبيعي الذي خلقه رب العالمين

عبد المجيد توفيق الكيوري
مندوب المجموعة السادسة

الاستجابة كولين متر موجود بالسوق لعدة اسباب



Prodrugs

Medicinal Organic Chemistry
and
Drug Design
By
Ass Prof .Mokhtar Al-Ghorafi

Prodrugs (Drug Latentation)

Many drugs have good activity in vitro, but when tested in vivo show weak activities. This was attributed to several factors such as

1. poor absorption (poor solubility)
2. rapid metabolism (easily oxidized)
3. poor access to the site of action.
4. Unpleasant taste (chloramphenicol, metronidazol, erythromycine).

The concept of prodrug was introduced to overcome these problems.

Prodrugs:

Biologically inactive compounds in vitro converted in vivo by enzymatic or non-enzymatic reaction into the active drug. ✓

Prodrugs must be:

1. Well absorbed.
2. Converted to the active drug in the body.
3. Non-toxic regarding groups released from the molecule.

التعريف
1- مركب دوائي
2- لا يكون له
نشاط دوائي
في المختبر
ولكن له
نشاط دوائي
في الجسم
بعد تحويله
إلى الدواء
النشط

بمستوى
الكيمياء
الطبية

۱- یزدن سراج

non-ionic $\text{C}_{12}\text{S}_{12}^{2-}$

Prodrugs are under taken to improve patient acceptability of the agent (i.e. reduce pain associated with administration) after absorption, alter distribution, alter metabolism, alter elimination.

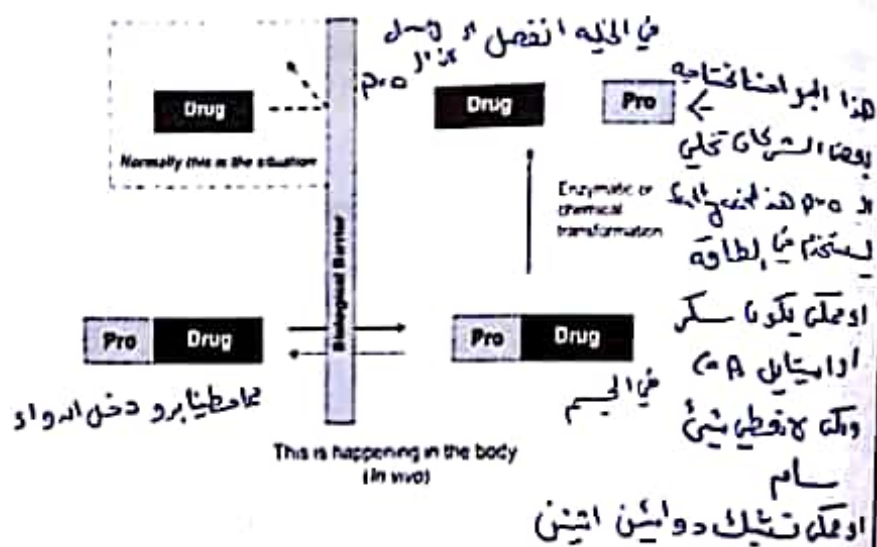
Advantages of prodrugs

- Increase absorption
 - Reduce pain at the site of injection
 - Elimination of an unpleasant taste associated with the drug.
 - Decrease toxicity
 - Decrease metabolic inactivation
 - Increase chemical stability.
 - Prolonged or shortened action.
- ان نيتك ادويه مع امصال
لدا واحد مثل ادوية الجرعونان

Decrease or increase

Action decrease or increase

بعض الاممانيات نيتك ادويه مع بعضها
ونمرضا كدوا واحد مثل ادوية كرمونات
والادوية السرطان



Classification of prodrugs according to functional group

The groups that are suitable for prodrug synthesis are:

1. Carboxylic acid group for ester and amide

2. Hydroxyl group for ester prodrug

3. Aliphatic and aromatic amine for amide

4. Carbonyl compounds containing prodrug.

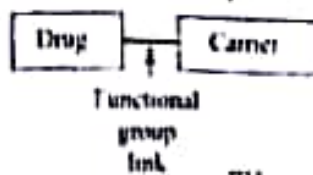
Functional group

Acids

Alcohols and phenols

Aldehydes and ketones

Amines



المجموعات التي تستخدم في تصنيع البرادروج

1) Carboxy
2) ester

Most common Prodrugs can be performed by

1. Esterification drug contain alcohol, carboxylic acid as prodrugs:

• Alcohol-containing drugs → acylation with aliphatic or aromatic carboxylic acids to ↓ water solubility [↑ lipophilicity] or with carboxylic acids containing amino or additional carboxylate groups to ↑ water solubility.

• Prodrugs of agents that contain carboxylic acid or alcoholic functionalities can often be prepared by conversion to an ESTER.

• This is the most common type of prodrug due to easy hydrolysis of ester giving active drug.

Hydrolysis is done by ESTERASE enzyme present in plasma & tissues.

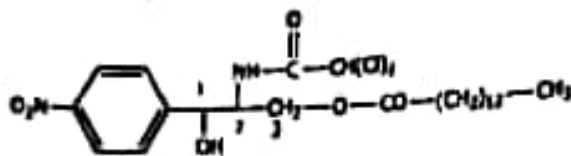
2. Amide formation with amino group

استخدام حمض الأمينو

لأنه يصل إلى
الأنسجة المستهدفة
بصورة كبيرة

Oc1ccc(cc1)C(C)(C)C(=O)O

Chloramphenicol Palmitate

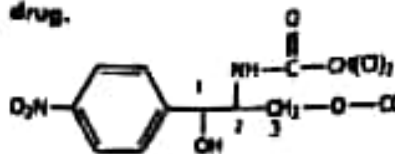


palmitic acid

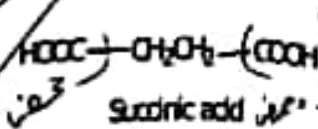
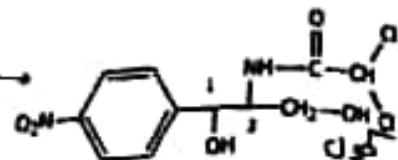
decrease solubility oral use

To OVERCOME BITTER TASTE

(for pediatric oral suspensions) → cleaved in duodenum to give active drug.



Chloramphenicol succinate



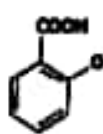
Increase solubility for LM injection

استخدموه الا قطريون وهو عبارة عن كون انفاك مع حمض يوضا حاد وما عدد الكربونات
ن 13 اظعم يقن وامتصاصه عالي
* هذا...

هذا الدواء ما يذوب في
الزيت والخل واما صافه فالي

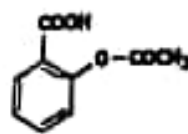
المواد الحافظة في الماء كثنائي ثيوداين نور - dimer, acceptor
 قيصح معاً مع مضمين الاون نور resonance والثاني resonance فاصح palen

2. Prodrugs masking drug toxicity & side effects:



Sulfonic acid

[Chem. 37, 15, from CH₂]



Aspirin
[ester of acetic acid]

Indicated in stomach by extreme volume

Almost devoid of gastric ulcer, rapid hydrolysis following absorption

يعرف حمض ديبالتالي كـ *glycolic acid* كما أن معناه حمضه ثنائي

فستان قفلاها بن انايلا فـمـج catalo salicylic acid producing

بوصف للم يتوقع لكم بين الـ *crystalline* و *amorphous* و *cyclic*

الفقه — تظہر فیہ عدم وجود ایضاً

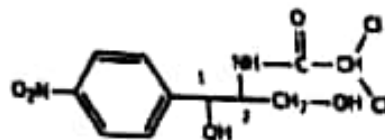
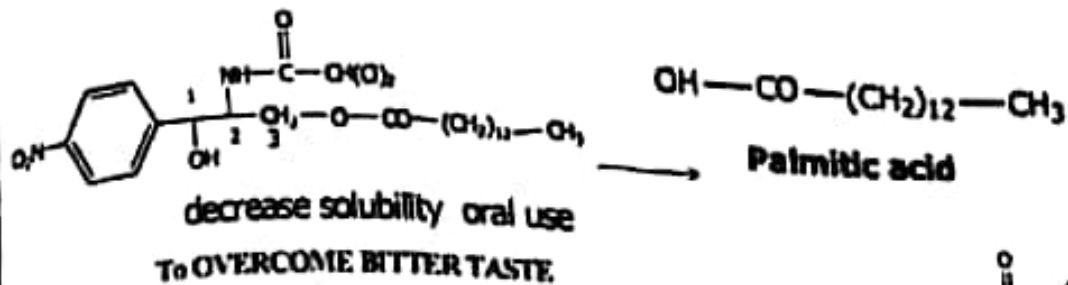
۱ ما اذا في ماد ما تى صلس قرحة

3. Prodrugs to mask bad taste:

E.g. Chloramphenicol [bitter taste antibiotic]

We make Chloramphenicol Palmitate or succinate which hydrolyzed quickly after swallowing.

N.B: succinic acid produced on hydrolysis is naturally present in body.



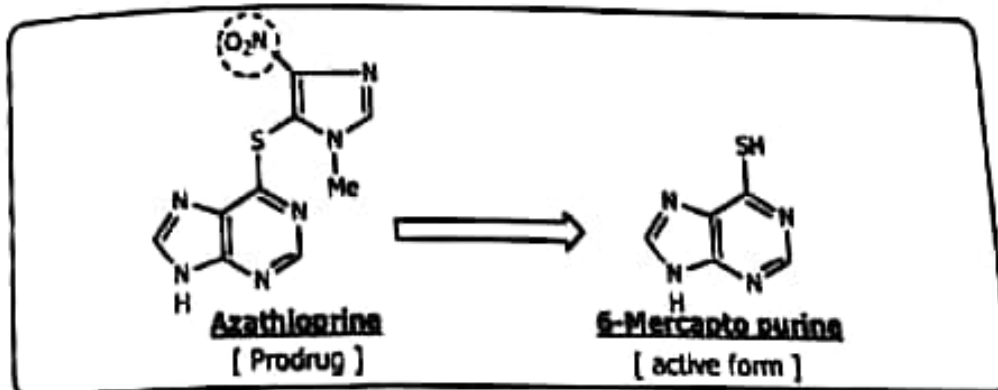
كأن هذا الدواء يصرف في صيغتين باليوم فليلاحظوا أنه حلقة (عبارتين المفروض) يظنوا حاجة حقيقة
عقار أو ester أو Carboxylic
فكما نظروا حلقة الدواء أصبح
معها أكسجين واذا فوجئنا مجموعة عليه أصبح الكبريت

4. Prodrugs for prolongation of drug action:

E.g.1:

6-Mercapto purine [short acting] so, → Azathioprine

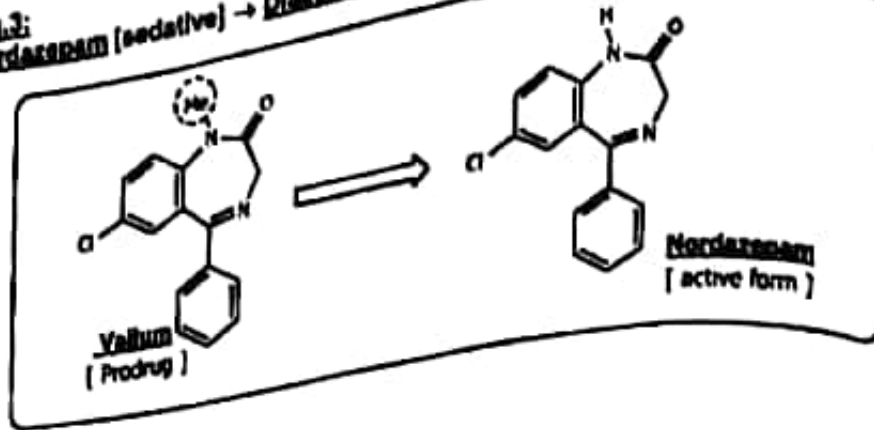
↑ Electron withdrawing power of the heterocyclic ring → faster release of the active form, so, NO₂ group in Azathioprine ensure a rapid efficient conversion of 6-mercaptor purine.



6-Mercapto purine suppresses the body's immune response and is therefore useful in protecting donor grafts. Unfortunately, the drug tends to be eliminated from the body too quickly.

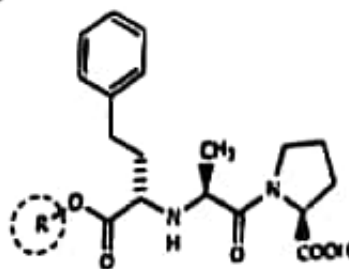
4. Prodrugs for prolongation of drug action:

E.g.3:
Nordazepam [sedative] → Diazepam [Valium[®]] which is a prodrug → N-demethylation



5. Prodrugs to improve membrane permeability

Enalaprilate: with COOH group which is important in binding via ionic or hydrogen bonding of the drug to the receptor BUT can't cross the fatty layer so → Enalapril [ester prodrug] which is hydrolyzed in blood stream by esterase enzyme.



R = H [Enalaprilate]

R = Et [Enalapril]

تتغل هذه الادوية على الـ
 و لا يسهل تحويل

اعراضه الجانبية rough day

بسر ما نغلبه day rough

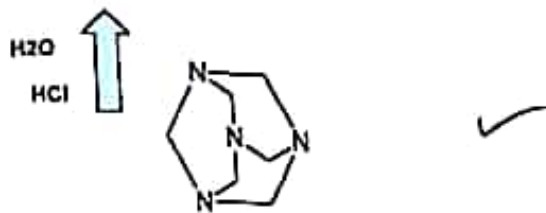
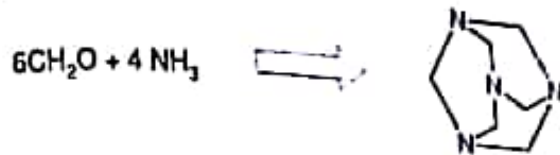
بسر ما نغلبه

المعروف باسم النجابين

6. Prodrugs used in targeting of the drug

Hexamine is a prodrug for formaldehyde used as urinary tract antiseptic; it's inactive at pH of the blood [slightly alkaline] so, it passes to urinary tract to be excreted in urine which is acidic due to the bacterial infection → degradation of hexamine to formaldehyde at the site of action.

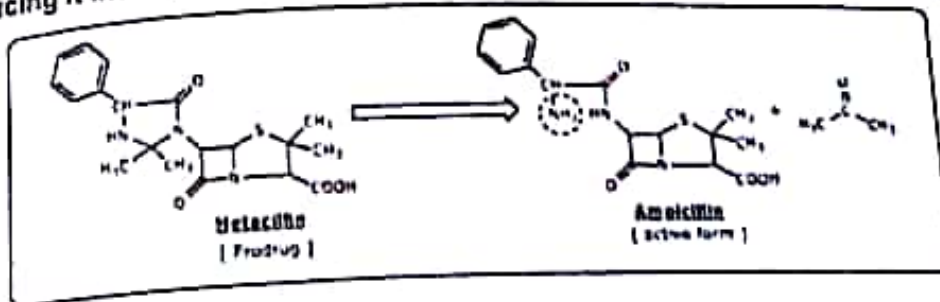
Synthesis of hexamine



7. Prodrugs used to ↑ chemical stability:

Intramolecular attack of β -lactam ring by the amino group in the side chain. So, we make:

Hetacillin which is a prodrug of ampicillin prepared to mask the amino group by introducing it into a ring [by acetone introduction] and it slowly releases ampicillin.



للقلب د - M2

لشغل كله و سطر يعني -ve

-ve
-ve

M1, M3

في بقية اعضاء

الجسم كامل

من غير ما تحدد

M1, M3

لكل الاثنين مع

بعض وظائف

Parasympathetic (muscarinic)

- cardiac output M2: decreases
- SA node: heart rate (chronotropic) M2: decreases
- cardiac muscle: contractility (inotropic) M2: decreases (atria only)
- conduction at AV node M2: decreases
- smooth muscles of bronchioles M3: contracts
- pupil of eye M3: contracts
- ciliary muscle M3: contracts
- salivary glands: secretions stimulates watery secretions
- GI tract motility M1, M3: increases
- smooth muscles of GI tract M3: contracts
- sphincters of GI tract M3: relaxes
- glands of GI tract M3: secretes

البارا خفي

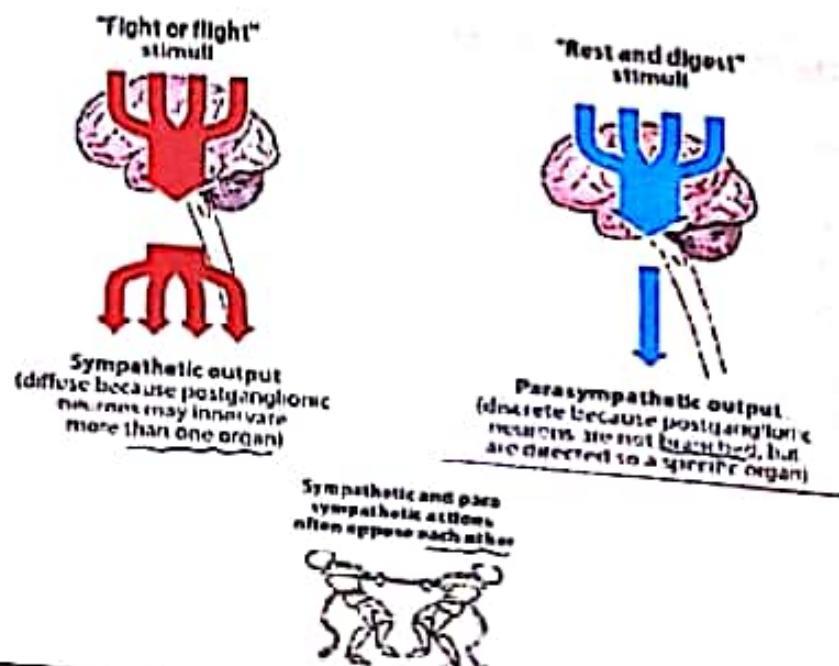
السما عميق

البار سطحي

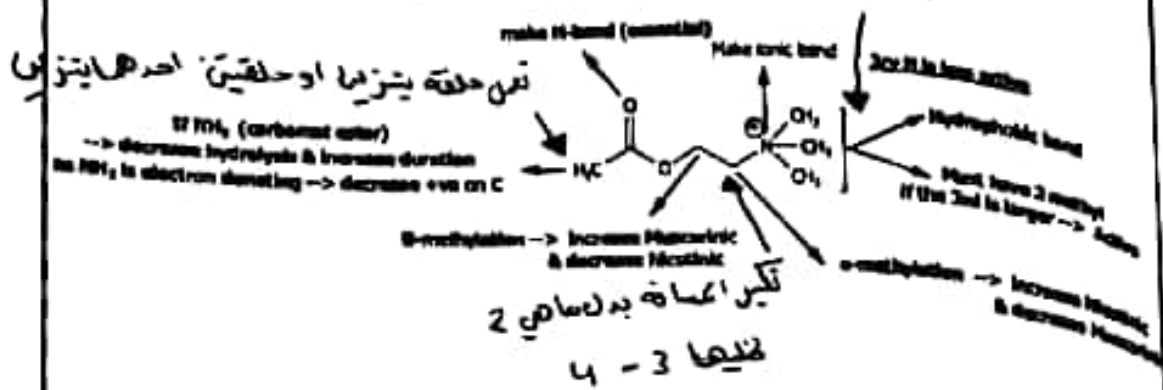
والسما عميق

(داخل)

Functions of the parasympathetic nervous system



بدل ماضي اليقاني كربونه بخلقه اليقاني cyclic حلقه او حويل



اذا استفنا دواء بهذه المواصفات نقول antagonist

بما ان مقي يكون الدواء nicotinic اكثر من muscarinic اذا كان β
 ومقي يكون nicotinic اكثر من muscarinic اذا كانت α

Acetylcholine

1. Decrease in heart rate and cardiac output
2. Decrease in blood pressure
3. Other actions

Acetylcholine is a poor therapeutic agent

1. Rapid hydrolysis of acetylcholine aqueous solutions particularly by acids and alkalis (poor oral bioavailability).
 2. Ionic properties make it water soluble but poorly absorbed across membrane
 3. In blood, it is liable to hydrolysis by esterase
 4. Acetylcholine is pharmacologically non-selective as it affects both nicotinic and muscarinic receptors
- It may be used to **produce miosis** in ocular surgeries by reconstitution immediately before direct instillation into the anterior chamber.

قائمة الأدوية إذا وجدنا H_2N ← هذه تسمى Carbenate

a. Direct-acting cholinomimetic

Methacholine	Carbachol	Bethanechol
<chem>CC(C)(C)C(=O)OC(C)(C)N</chem> مادم 12 بيتي 14 م short → increase M effect & decrease N effect → decrease hydrolysis with esterase M selective	<chem>CC(C)C(=O)OC(C)(C)N</chem> long decrease hydrolysis but not selective	<chem>CC(C)C(=O)OC(C)(C)N</chem> long decrease hydrolysis → oral active increase M & decrease N
Used as racemic mixture for <u>glaucoma</u> . Because S is 3 times less hydrolyzed than Ach & R is competitive inhibitor of Ach.	- Uses: <u>Glaucoma</u> <u>Urine retention</u> <u>Intestinal atony.</u>	- Uses: post surgical urine retention & intestinal atony

All of the direct-acting cholinergic drugs have longer durations of action than acetylcholine.

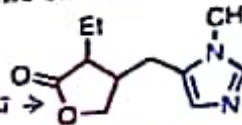
بما ان يحصل لهذا الدواء (تأثيره) يكون له اثار جانبية :-

يعمل هذا الدواء
بسرعة

a. Direct-acting Cholinomimetics

ii. Alkaloids

- Pilocarpine is the classical example



pilocarpine

3-ethyl-4-((1-methyl-1H-imidazol-5-yl)methyl)-
dihydrofuran-2(1H)-one

- Chiefly used in eye drops to lower intraocular pressure in chronic simple glaucoma (due to its miotic effect)
- Stability of pilocarpine
 - Opening of lactone to pilocarpic acid
 - Epimerization at C3 to epipilocarpine
 - Thus the gel and/or solution should not be used 2 weeks after dispensing and kept refrigerated.

Some of the more therapeutically useful drugs (pilocarpine and bethanechol) preferentially bind to **muscarinic receptors** and are sometimes referred to as **muscarinic agents**

1- Glycopyrronium

2- Trospium

3- Vagotonic

4- Anticholinergic

5- Anticholinergic

6- Anticholinergic

7- Anticholinergic

8- Anticholinergic

9- Anticholinergic

10- Anticholinergic

11- Anticholinergic

12- Anticholinergic

13- Anticholinergic

14- Anticholinergic

15- Anticholinergic

16- Anticholinergic

17- Anticholinergic

18- Anticholinergic

19- Anticholinergic

20- Anticholinergic

21- Anticholinergic

22- Anticholinergic

23- Anticholinergic

24- Anticholinergic

25- Anticholinergic

26- Anticholinergic

27- Anticholinergic

28- Anticholinergic

29- Anticholinergic

30- Anticholinergic

Some adverse effects observed with cholinergic drugs.



b. Anti-choline esterase: Indirect acting

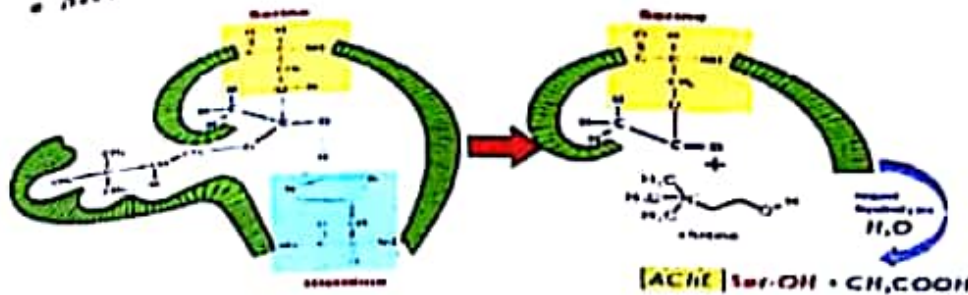
Anticholinesterases (Reversible)

Acetylcholinesterase is an enzyme that specifically cleaves acetylcholine to acetate and choline and, thus, terminates its actions. Inhibitors of acetylcholinesterase indirectly provide a cholinergic action by prolonging the lifetime of acetylcholine produced endogenously at the cholinergic nerve endings. This results in the accumulation of acetylcholine in the synaptic space.

b. Indirect-acting Cholinomimetics

Cholinesterase Inhibitors (Anticholinesterases)

- Mechanism of enzymatic cleavage of ACh



ممکنه تعطل ادریه توقف تکثیر الاستایل کولین یعنی تعطل د وادیت عمل الانزیم الذی یکس الاستایل کولین
 می حاله اتسمم باکاتروپین
 ماله اکتس الا قردیم

Reversible AChE-inhibitors

- Therapeutic Uses
 - myasthenia gravis
 - to stimulate the bowels and bladder after
 - antidote to competitive neuromuscular blocking agents
- They act by carbamylating the **serine** moiety at the active site of AChE ($Ser-OH \rightarrow Ser-O-C(=O)NR_2$)
- Examples



Concentration of
muscle tissue



vision

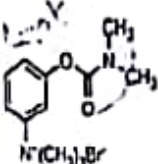


BP

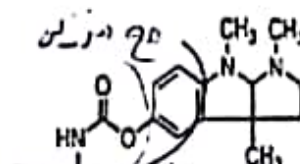


Heart rate

Some actions of physostigmine



neostigmine bromide
orally active
does not cross BBB



physostigmine
tertiary amine
shows CNS side effects
improves cognitive function in
Alzheimer-type dementia

حلقه بنزین
 کیف اثر می کند
 اکتیو است
 Neostigmine

اذا كان معالجاً مع استماتة مع حلقه بنزین
 مباشرتاً الخرق ای الاله واهلو
 Neostigmine

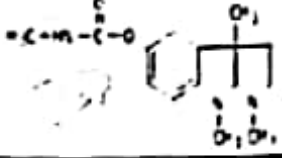
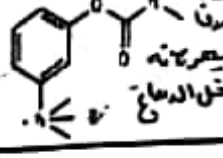
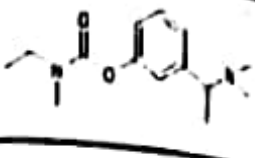
حلقه بنزین
 کدها
 اکتیو است
 Physostigmine

هذا الدواء زود و له کربونات یعنی
 کثافت یدخل الدماغ و یعالج زلزال
 و لكنه احنا یهضمنا الاصل
 الذی هی حلقه بنزین مع استماتة

فیزو و نیرو ورفا

میرد دینرو ورفا Reversible

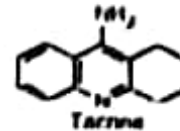
a. Aryl carbamate (enzyme substrate)

Physostigmine	Neostigmine	Rivastigmine
 میرد دینرو ورفا	 میرد دینرو ورفا	 میرد دینرو ورفا
Uses: - Alzheimer (non-polar) - Glaucoma - atropine toxicity	Uses: <u>Myasthenia gravis</u> → <u>polar</u> (NOT in Alzheimer)	Uses: <u>Alzheimer</u> (brain selective) → non-polar

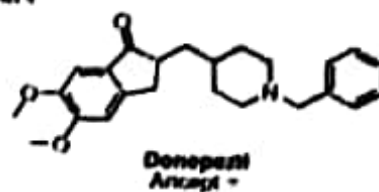
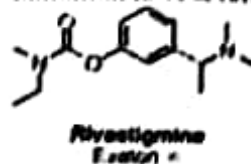
میرد دینرو ورفا
میرد دینرو ورفا

AChE Inhibitors and Alzheimer Disease

- Tacrine was reported for the relief of Alzheimer disease but this advantage was outweighed by its hepatotoxicity



- Currently two drugs are marketed for use in Alzheimer's disease.
 - Donepezil is considered AChE inhibitor, more selective to central AChE rather than peripheral one
 - Rivastigmine is considered 'pseudo-irreversible' since inhibition lasts several hours

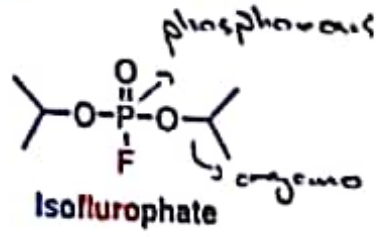


الغشاء نزلوا دواء العين (قطر العين) اسمه

Organophosphorus compound

Irreversible AChE-inhibitors

- They are organophosphate compounds having the capacity to bind covalently to acetylcholinesterase.
- Example



organophosphate compound

Therapeutic Use :

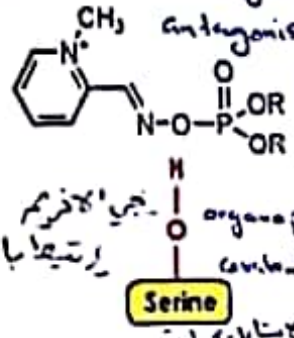
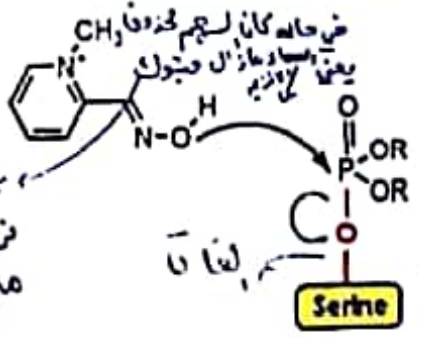
- ophthalmic ointment is used topically for the chronic treatment of open-angle glaucoma.
- The effects may last for up to one week after a single administration.

ما هو مخرج الشخص الذي شرب سم قاتل السم يرتبط بالاسيتايل كولين سمه كانه AChE والدم انه يرفع مع الاسيتايل كولين يكسب حاله جدا (يتركز عالي) فلما نقول شخص شرب سم القاتل كانه اخذ جرعة عاليه من AChE ينشأ ويتم تثبيط AChE الذي يكسب الاسيتايل كولين

Treatment of Organophosphate toxicity:

Antidote for AChE-inhibitors toxicity

- Pralidoxime (PAM), can regenerate the enzyme, if used before aging (6-8hrs)



- Atropine is used in emergency to reverse signs of AChE inhibitors intoxication (doses up to 100mg/day, preferably divided as atropine is toxic itself)

التسمم بالقاتل

القاتل هو الذي اساس يرتبط بالانزيم يعيد الدواء يربط بالانزيم وبالتالي يمنع ارتباطه بالسم

الأتروبين لا يصرف للأطفال حديثي الولادة ولا
 يصرف لكبار السن الذي يكون لديهم prostate
 لخطر احتباس البول وارتفاع ضغط الدم

الأكثر انتشارا بعد الأدرينالين

d. Muscarinic Antagonists (Parasympatholytics)

• Their action is competitive (depends on their concentration and relative affinity to receptor)

• Actions and Uses

- GIT $\rightarrow$ antispasmodic
 - Decrease GIT motility $\rightarrow$ antispasmodic
 - Relief of biliary colic
- Urinary Tract $\rightarrow$
 - Antispasmodic in renal colic
 - Treatment of urinary incontinence and nocturnal enuresis in children
- Bronchi $\rightarrow$
 - Bronchodilators in bronchial asthma

- Eye

- Mydriasis, contra-indicated in glaucoma $\rightarrow$ لا يصرف في حالة الزرق
- Loss of light reflex
- Cycloplegia and loss of accommodation for near vision, useful in fundal examination

- CVS

- Increase heart rate
- Increase conduction at AVN so used in heart block

- CNS

- Stimulation of respiratory centre $\checkmark$
- Restlessness, hallucination and delirium $\checkmark$
- Anti-emetic (inhibition of CTZ)
- Anti-parkinsonian effects
- Antidote for organophosphorus intoxication

الأتروبين يوسع الشعب الهوائية ويزاد الأثر بزيادة الجرعة

الأدرينالين يعالج anaphylaxis ولكنه لا anticholinergic أفضل لأنه agonist $\rightarrow$ symp أقوى من antagonist para
 ولا يملك على القلب ادرينالين أفضل من الأتروبين هو فقط مضاد

Atropine side effects

- 1- Dry mouth
- 2- Blurred vision
- 3- urinary retention
- 4- Tachycardia

must be large hydrophobic to make hydrophobic bond with the receptor (umbrella effect) $\rightarrow$ Inhibit Ach approach

one of R1 & R2 may be aromatic & 2nd saturated cycle

تقن بنزينة

3-4 نرد هامة
 Ethylene bridge (essential)

البياتي

Et or Propyl (propyl more active)
 خليها البياتي حلقا او سلسلة

Ionic bond $\rightarrow$ so, quaternary N more active (may be 3ry & protonated at physiological pH)

H-bond $\rightarrow$ may be ester or amide or alcohol

3-4 اذا اردت ان تقسم دواء antagonist فقط تكبر

منه وجوب تقابل

Atropine side effect

- Dry mouth
- Blurred vision
- urine retention
- Tachycardia

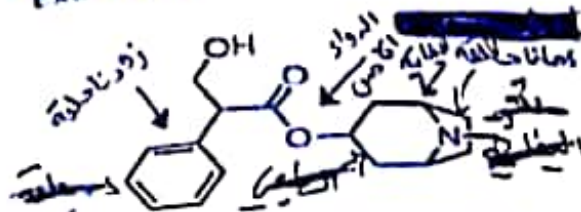
III. Anti-Cholinergic

1. Muscarinic Antagonist

Action:

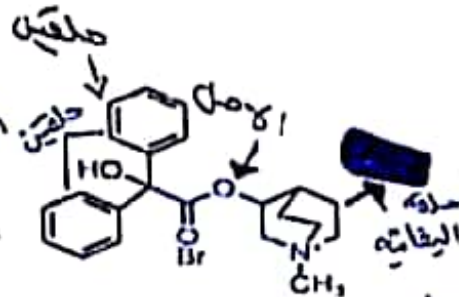
1. Anti-spasmodic (relax smooth muscle of GIT & Urinary tract)
2. Mydriatic (dilatation of eye pupil)
3. Decrease gland secretion (anti-ulcer & decrease sweating)
4. Bronchodilators.

a. Muscarinic Antagonists Examples



Atropine (Isopto-Atropine E.D.)

Prototype muscarinic antagonist
Typically used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils.
Antidote for organophosphate poisoning
Treatment of heart block
Hallucinogenic, thus contraindicated



Clidinium bromide

Used with
→ chlordiazepoxide
(tranquilizer) for
spastic colon
(Librax)

نسيجه ايجيانه مير اوان

IPs قابلية

نتيجة درجيا

مايسين

ادمان

كان فيه

Chlorodiazepoxide

ايدو

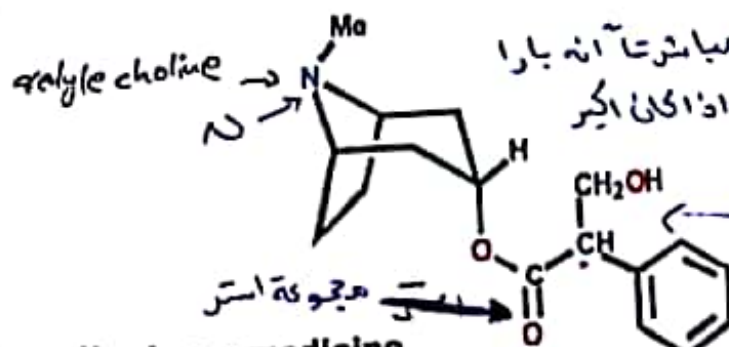
هذا الدواء لا يؤخذ يوميا

لنفسه او ما يشد به

لنفسه او ما يشد به

12. Cholinergic Antagonists (Muscarinic receptor)

12.1 Atropine

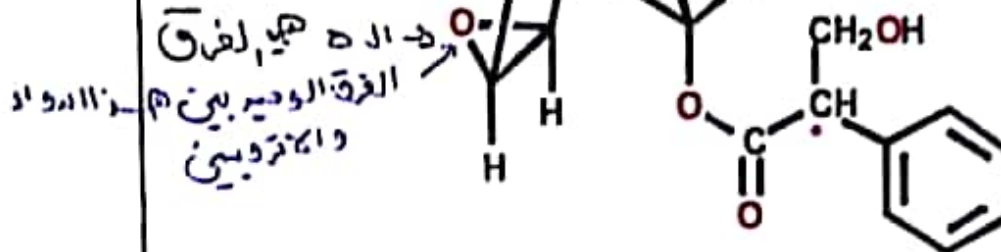


- Used as a medicine
decreases GIT motility
antidote for anticholinesterase poisoning
dilation of eye pupils
- CNS side effects - hallucinations

Cholinergic Antagonists (Muscarinic receptor)

Hyoscyine (scopolamine)

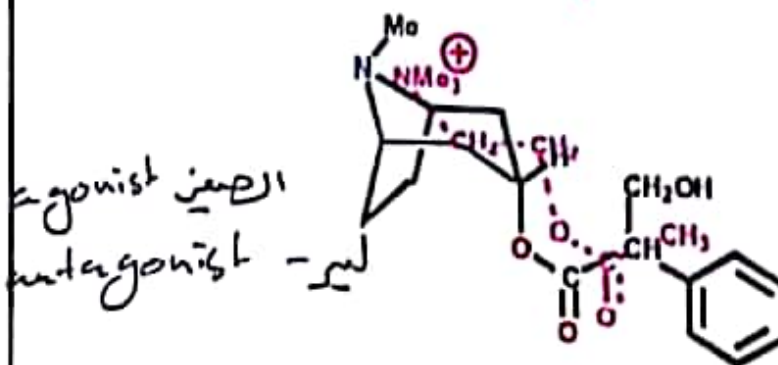
الفرق بين هذا الدواء والبارالدين
هنا فقط ان هذا الدواء



لما يكونا معاً مثلاً كبريتات (البرين هو agonist والبارالدين هو antagonist)

Cholinergic Antagonists (Muscarinic receptor)

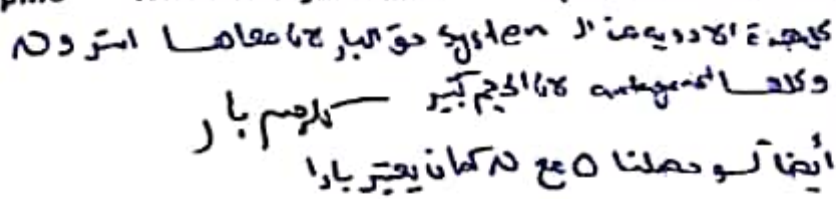
Comparison of atropine with acetylcholine



- Relative positions of ester and nitrogen similar in both molecules
- Amine and ester are important binding groups (ionic + H-bonds)
- Aromatic ring of atropine is an extra binding group (vdW)
- Atropine binds with a different induced fit - no activation
- Atropine binds more strongly than acetylcholine

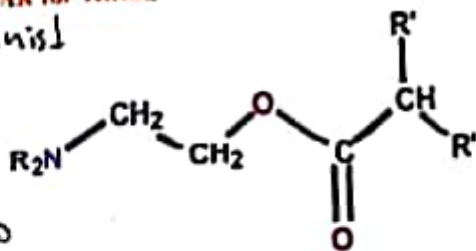
የጥገናና ማረጋገጫ

pharmacophore = ester + basic amine + aromatic ring



Antagonists (muscular) agonist syn

Agonist



K = Aromatic or
Heteroaromatic

Sympa-Agonist
aromatic or
heteroaromatic
پیچیده
حلقه اروماتیک

- Tertiary amine (ionised) or a quaternary nitrogen

- Tertiary amine (ionised) or a quaternary nitrogen
- Aromatic ring
- Ester
- *N*-Alkyl groups (R) can be larger than methyl (unlike agonists)
- Large branched acyl group
- R' = aromatic or heteroaromatic ring
- Branching of aromatic/heteroaromatic rings is important

SAR for Antagonists

Tertiary amine (ionised)
or quaternary nitrogen
Aromatic ring
Ester
N-Alkyl groups (R) can be
larger than methyl
R' = aromatic or heteroaromatic
Branching of Ar rings important

عفا 5

SAR for Agonists

Quaternary nitrogen

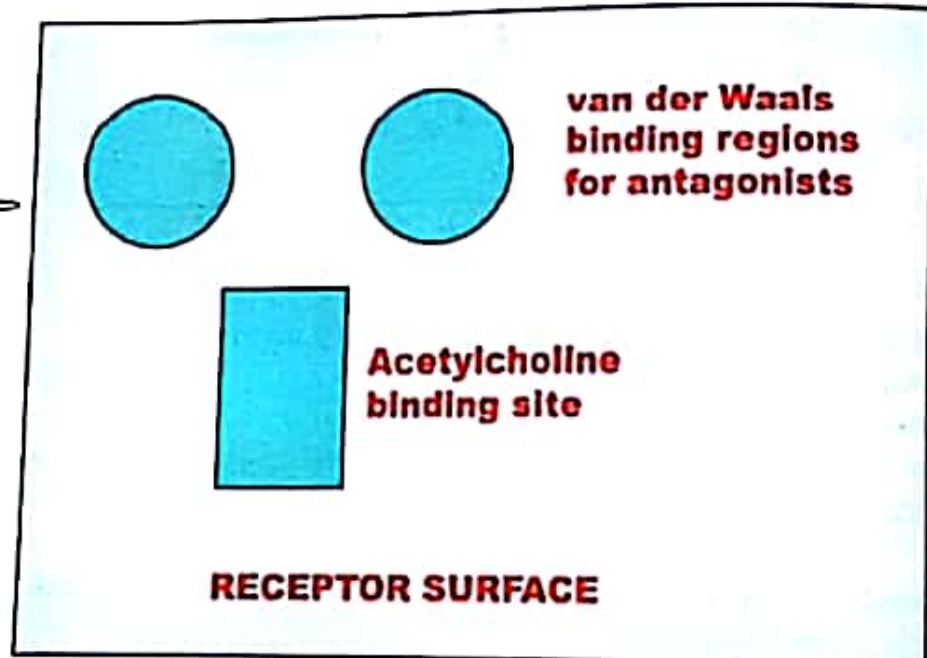
Ester
N-Alkyl groups = methyl

R' = H

Cholinergic Antagonists (Muscarinic receptor)

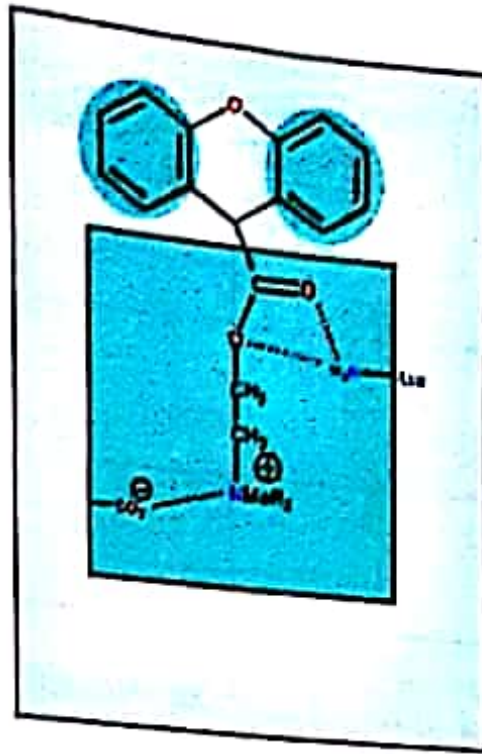
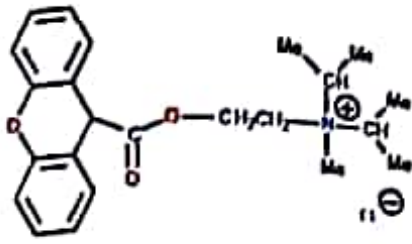
Binding Site for Antagonists

ضيق منطقة كتمان يصح ارتباط الاستاين كولين
فأصبح blocker



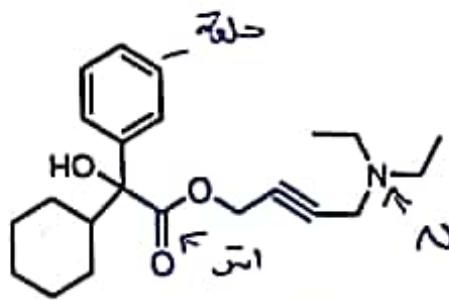
حالة ى
الفا ضي
حالة بعى
blocker
مناجج
acetyl
choline

Binding Site for Antagonists



هذا الدواء عبارة عن حلقة و ester
يعالج التبول الا ارادي كمنه الا لطفان
ويعالج التبول الليلي
ويعالج ايضا عدم القدرة على التبول
(يفلق ال sphincter ويرخي العضلات)
* التبول الدارادي يعني ان لا ينفق منه
البارازات

a. Muscarinic Antagonists Examples



Oxybutynin (Uriban®)

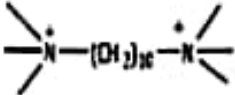
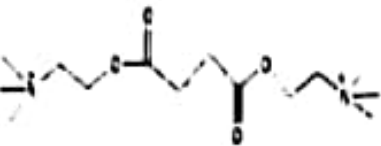
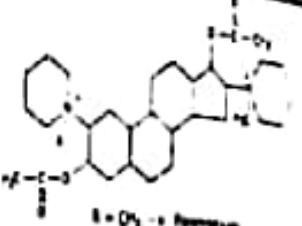
1. management of urinary frequency, urgency and urinary incontinence
2. nocturnal enuresis

* لوزادت الجرعة يحل
هلوبة

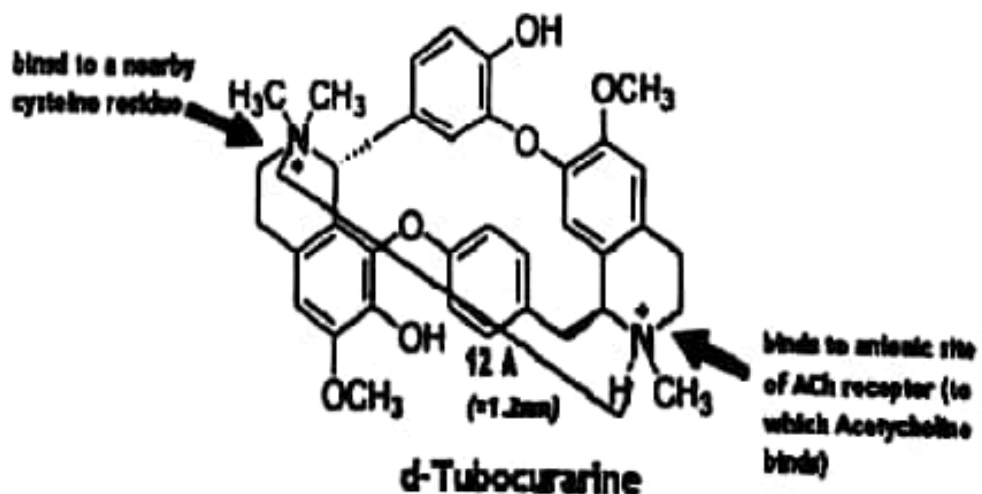
جرعة عالية تسببها لو استنش

Nicotinic Antagonist

- Used as Skeletal muscle relaxant - adjuvant to general anesthetics to ↓ dose.
- d-tubocurarine (parent) → distance between 2 N⁺ → 1.2 nm (one of them bind to anionic site & the other bind to nearby cysteine residue)

Decamethonium Chloride	Suxamethonium Cl	Pancronium & Vancronium
		
Duration = 45 min With <u>side effect</u> on the heart ↓ H.R & B.P	<u>Ester</u> → <u>easy hydrolysis</u> (5 min duration) but with side effect also	<u>Steroid spacer between 2 Ach moieties</u> → Rapid onset & long duration = 45 min → with no effect on B.P.

Prototype blocker : d-Tubocurarine (SAR)

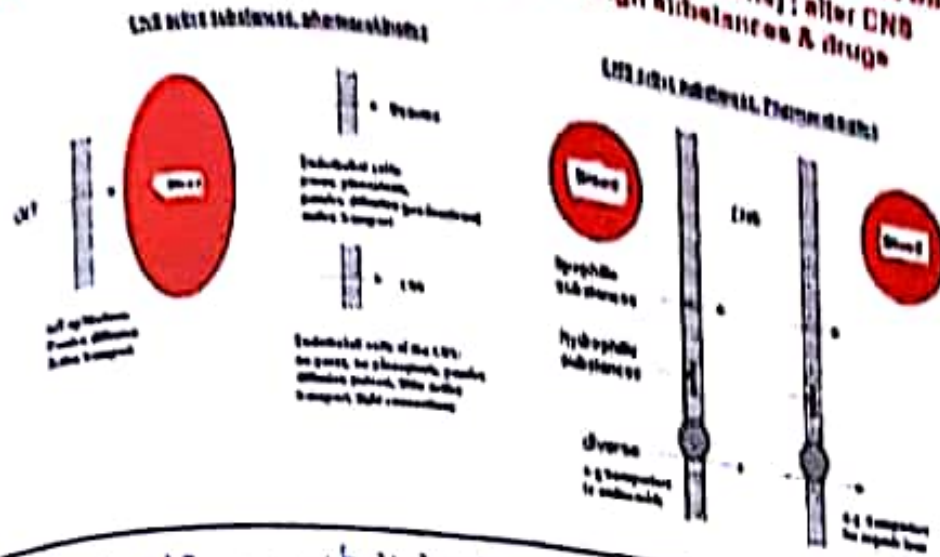


compounds having 2N⁺ keeping 1.2nm distance are good antagonists

CNS Drugs

CNS = Brain + Spinal cord.

Any material to give CNS effect should be with high lipophilicity to pass BBB
 Damage to CNS endothelial cells by toxins (if CNS infections); after CNS permeability selectivity → allow passage of foreign substances & drugs



اگر در این حالت یا او ضربه ای می خورد یا عفونت می شود و دقت در این

حاجه زنده نگه داشتن
 حاجه زنده نگه داشتن

CNS Acting drugs

CNS depressants

- Sedative - Hypnotics & Anxiolytics.
- General anaesthetics [Local anaesthetics].
- Anti-convulsants. کربامید
- Anti-psychotics.
- Centrally acting skeletal muscle relaxants.
- Anti-Parkinsonism agents.

acetylcholine
 Depress

اواچیناژ

CNS Stimulants

- Analeptics [Respiratory stimulants].
- Psychomotor stimulants.
- Anti-Depressants.
- Xanthines

انقباض

حاجه زنده نگه داشتن

حاجه زنده نگه داشتن

Central (brain) neurotransmitter (NTs)

Amino acids

Gamma amino-butyric acid (GABA):

- The major inhibitory NTs in the CNS
- Act on both GABA_A (Ligand gated ion channel, Cl⁻ channel) and GABA_B (G-proteins to potassium channels) receptors.
- Benzodiazepines (BDZs) act by enhancing the action of GABA
- Inhibitory effects are blocked by Picrotoxin (noncompetitive antagonist for the GABA_A receptor)

Glycine:

- Inhibitory NTs in spinal cord
- Act on Glycine receptor (GlyR) → opening Cl⁻ channels.
- Strychnine selective glycine receptor blocker.

Aspartate and glutamate:

- Both are excitatory NTs in CNS.
- They act on N-methyl-D-aspartate (NMDA) receptor.

الاستروجين
والجليب

الجليب والسيامين
كل

Norepinephrine

- Regulation of arousal and mood.
- Increased released responsible for wakefulness and alertness.
- Deficiency may cause Depression

Dopamine

- Motor function: deficiency, causes Parkinson's disease
- Control & behavioral function: Increased activity causes Schizophrenia
- Endocrine function: dopamine stimulates GH from pituitary gland, hypoprolactinemia and precursor to adrenaline and noradrenaline
- Causes nausea and vomiting by stimulating dopamine receptors in CTZ
- Increase in sexual desire, or anticipating pleasurable activity

CTZ, Chemo receptor Trigger Zone

Serotonin (5-HT)

Control of mood, body temperature, behavioral changes, hallucinations and wakefulness, appetite, sexuality.

Low levels of 5-HT is associated with *depression* and *migraine*

Acetylcholine

- Mainly M1 receptor is predominant among M&N receptors.
- Affect arousal, learning, motor control and short term memory.
- Hyperactivity may cause (*Parkinson's disease*).
- Loss of cholinergic neurons may cause (*Alzheimer's disease*).

Mania → معناه جنان

في الاكثاري في ناس سعادتها و في ناس uniform
اذا نقص السور والسيروتونين وناس يقولوا اتوية مع ليدو بامين
اذا ارتفع السور والسيروتونين تعمل جينات

اول دواء نزل
جبارة سائلة

CNS Depressants

1] Sedative , Hypnotics & Anxiolytics

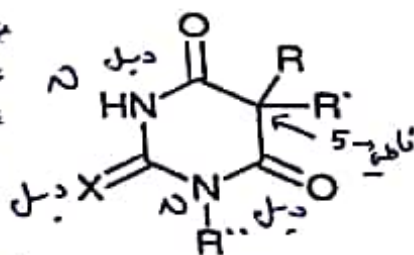
Action from **slight sedation** to **sleep** according to the **drug used** ,
dose, **duration** & **its route of administration**

Classified into :

- 1.Barbiturates.
- 2.Benzodiazepines.
- 3.Miscellaneous compounds

Barbiturates

* لو عملت مكانا الخنثى حلقه بنترين ريج
* ولو عملت ديل او متفرقة تصيح intermediate
* ولو عملت اليقاني ريج short
* ولو عملت مكانا اذ ريج ultra-short

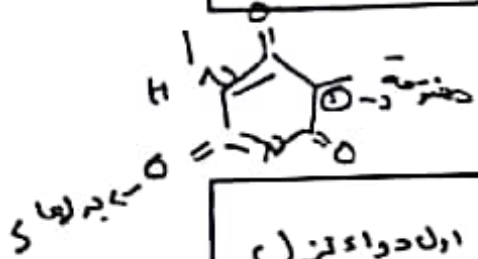
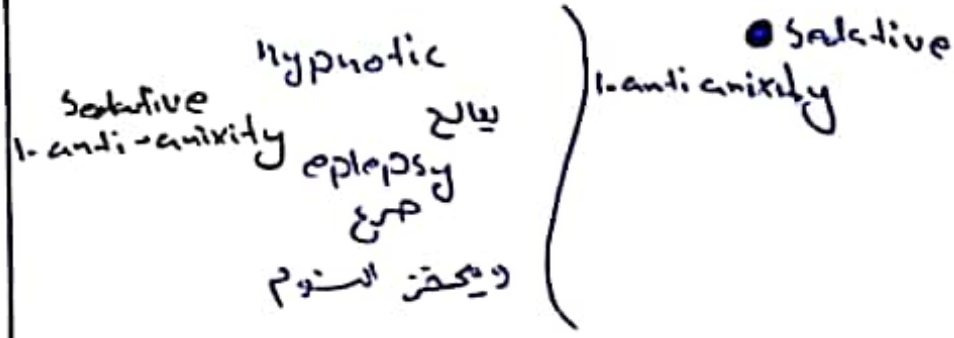


* وما يكون كفا جيني
inactive يعني

جرع عكليه - A sedatives a drug that produces a relaxing, calming effect. make the patient drowsy, they usually do not produce sleep. Sedatives are usually given during daytime hours

جرع عاليه - A hypnotic is a drug that induces sleep.

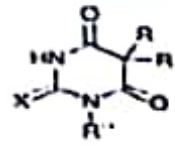
Sedative- hypnotic drugs : S.D (Sedative) , In large dose(hypnotic)



Barbiturates

اول دواء نزل

[i] Barbiturates

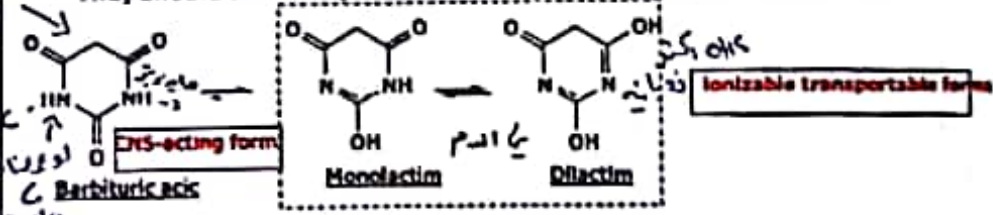


M.O.A : By potentiating of inhibitory effect of GABA by allosteric modulation of GABA_A receptors.

Properties :

• They should be weakly acidic & undergo lactam-lactim tautomerism.

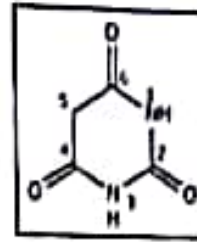
Handwritten notes in Arabic: 'عمل برين و تبادل' (action and exchange), 'ادوية هادئة' (sedative drugs), 'تأثيرها' (effect), 'لرئيس كايه' (main effect), 'ادوية هادئة' (sedative drugs), 'واكلها' (eat it), 'اذا ما قش' (if you cut), 'فاده اقص' (maximum benefit).



• There should be a balance between the hydrophilic blood transportable form and the hydrophobic CNS-acting form. As barbiturates are taken up by CNS, equilibrium tends to shift to the left. Acidity result from the ability of N to lose H & stabilization of the resulting anionic charge of conjugate by resonance delocalization

ساختار

SAR:



1. C₅ hydrogen atoms must be substituted

2. Introduction of halogen atom into 5-alkyl subs → ↑ potency.

3. Introduction of polar gp (OH, NH₂, RNH, CO, COOH & SO₃H) to 5-alkyl gp → ↓ lipid sol → destroy the potency

II. N atoms:

1. Methylation of **N1** or **N3** → ↑ lipid solubility → quick onset & short duration (↑ metabolism)

2. Substitution of **both** N atoms → non-acidic → inactive. [no transportation in blood].

3. Large alkyl group → Anti-convulsant properties.

-Replacement of O with S → ↑ lipid solubility ↑ rapid onset and short duration

حفظه در الیوم
index
منیویجا
لوزودنا الحرفه
قدیدخ الشخص
respiratory depression

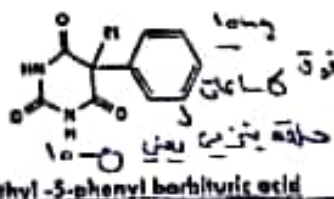
Classification of barbiturate

1. Long acting (>6 hrs)

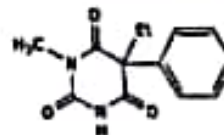
* High lipid sol leads to induce the drug to liver, lead to increase of its metabolism
1- increase in CNS activity.
2- decrease in onset (i.e. faster action)
3- decrease in duration of action (faster metabolism)
4- increase in protein binding

1. Long acting (>6 hrs)

Phenobarbital



Mephobarbital



5-Ethyl-1-methyl-5-phenyl barbituric acid

They are typically anti-convulsants [bulky substituents]. With slow onset (30-60 min.) & relatively long duration.

Typically Anticonvulsants,

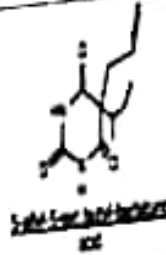
تسكن
ادوية
ضبابه
الصرع

لوسا
شوت
دکتر
فمنزاد
تعلی
للمر
indication
یعنی ترفیع الزیما
الکلیه
کدری به البهارسیا
ترشح الزیما
الکبد
واد لیسول
لرطه جرح

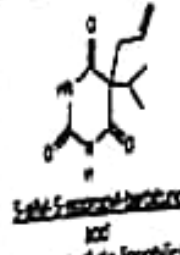
سقوط
باربیتور

2. Intermediate acting (3-6 hr) [with branched unsaturated side chain]

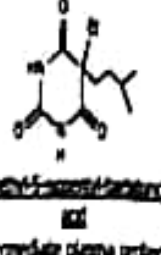
Fullbarbital



Apobarbital



Amobarbital



With slow onset (45-60 min) & intermediate duration → with intermediate lipophilicity & intermediate plasma protein binding (50%)

Sedative/Hypnotics, relatively slow onset (45-60 minutes) and intermediate duration (3-6 hrs).
They are of intermediate lipophilicity and intermediate plasma protein binding (50%)

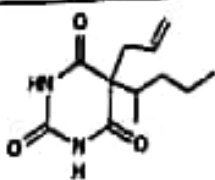
دخول به تدریج بالا و در حد متوسط
و اکتیوایزوم بالا

1- live + enzyme
2- respiratory depression
3- addiction

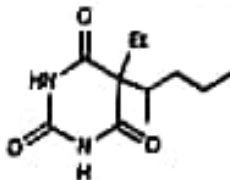
لیرمات که دواد حدت که ساعت و معافه تفسیر (کوتاه)
protein binding

3. Short acting (< 3 hr)

Secobarbital



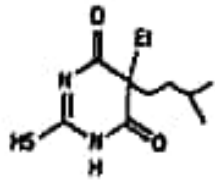
Pentobarbital Na



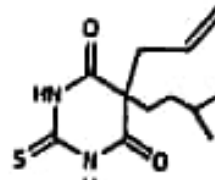
Typically hypnotic, with rapid onset (10-15 min) & short duration → with ↑ lipophilicity & ↑ plasma protein binding (70 %)

4. Ultra short acting (G.A) (10-30 min.)

Thiopental



Thiamylal



Administered by injection (as salts), for induction of anaesthesia with immediate onset (10 sec) & very short duration → with ↑ lipophilicity & ↑ plasma protein binding (>70%)

1- live + enzyme
2- respiratory depression
3- addiction

قلنا
دخول به تدریج بالا
و اکتیوایزوم بالا

activity

Disadvantages of barbiturates:
Narrow therapeutic index (respiratory depression, death)

- ↑ hydrophilicity → ↑ excretion [↓ activity]
- Barbiturates are Enzyme Inducers: Addicltion, Tolerance, Drug-Drug interaction [with Oral contraceptives, Warfarin → ↑ dosage → ADDICTION + DRUG-DRUG INTERACTIONS]

Benzodiazepines [BZPs]

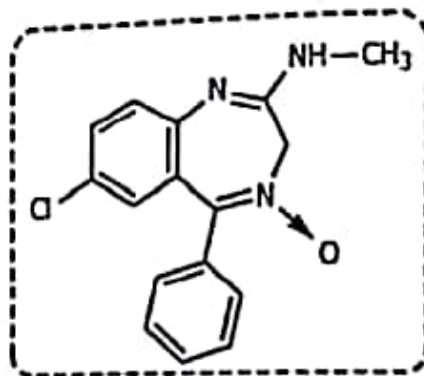
History:

• Discovered by SERENDIPITY. (exploring the unexpected or discovering things not intended to) It is an official way of drug discovery (like penicillin).

في اد diazepam له حضرة كادفوا
ان لتقابل تغيري رجوع بي اي
فوجهوا انه ليس نوم وهو اقن منا
الكل barbitals

Chlordiazepoxide

منوع حرقه الا بوصفه



بي اي
بشكل عام يدخل الدماغ
و يعمل

1- depress
2- Decrease
و نقص

هذا يخلط clinidiazepam
واحد المفضل و واحد

للقولون العصبي هذا يوقف
الدماغ والمثالي يوقف قمتا العضو

استخدامه قوي جدا يومية قد يعمل بقود

Depress

Decrease

نقص

heroin و morphine و diazepam افق نادمان او

Benzodiazepines [BZPs]

M.O.A: allosteric binding to $GABA_A$ receptors with $GABA$ agonistic action [DIFFERENT SITES FROM BARBITURATES]

[$GABA \rightarrow$ CAN'T CROSS BBB]

BZPs: enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor,

Uses:

Anti-Anxiety, premedication & induction of anaesthesia, Insomnia,
Anti-convulsants [Diazepam, Clorazepate & Clonazepam], Skeletal muscle relaxants.

Advantages over barbiturates:

- No respiratory depression with over dosage.
- Fewer drug-drug interactions [Barbiturates are enzyme inducers].

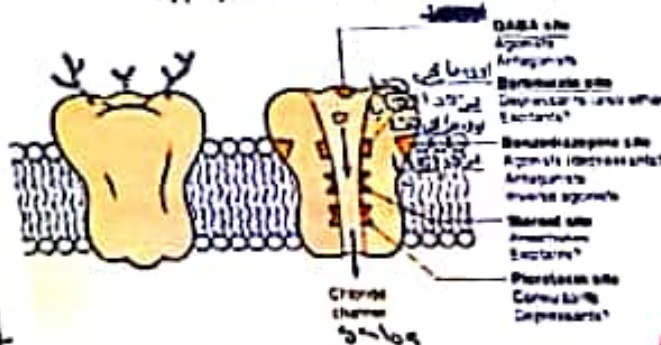
او باجي او Benzo يزود لقاس

و كدر او باجي يزود لقاس

لر و كدر او باجي يزود لقاس

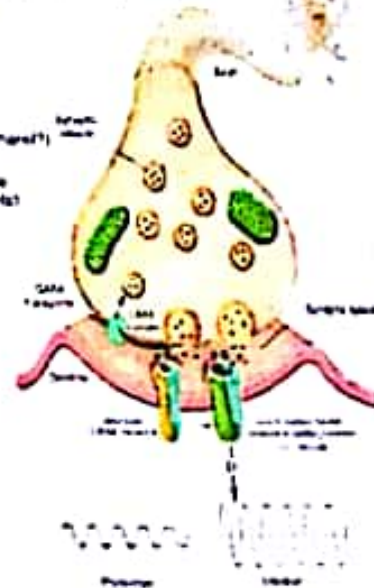
Mechanism of action :-

- BDZs potentiate the action of $GABA$ by binding to BDZs site on $GABA_A$ receptors $\rightarrow$ increasing their affinity for $GABA$.
- This results in an increased opening of Cl^- channels and enhanced hyperpolarization $\rightarrow$ Sedative effect.



Actions of BDZs :-

- Minor tranquillizing action (Anxiolytic).
- Sedative and hypnotic effect.
- Anticonvulsant and antiepileptic action.
- Anesthetic action.
- Slight effect on CVS and respiration.
- Slight muscle relaxant action.



استخدامات - Clinical (Therapeutic) uses :-

- Anxiety disorder (long-acting drugs)
- Sleep disorder (short-acting drugs)
- Epilepsy (Seizures)
- Muscle spasm and rigidity
- Pre-anesthetic medication
- Alcohol withdrawal syndrome



- Adverse effect :-

- Drowsiness, confusion and ataxia.
- Chronic use of high doses produces tolerance and dependence.
- Respiratory depression and hypotension.

- BDZs antagonist :-

Flumazenil (Anexate)

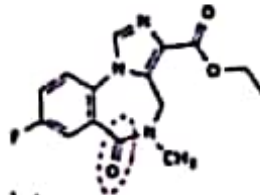
- It is a GABA receptor antagonist.
- It is given by IV administration only because of its high hepatic first-pass metabolism.
- Short duration of action used by repeated injection.

anti-dot

Disadvantages :

- Addiction [metabolized to active agents , causing **hang over** on accumulation] → [Still feels **drowsy after waking up** from sleep due to **extended effect** of the drug]
- Toxic if co-given with alcohols.

Anti-dot [if Intoxication occur] is **Flumazenil(anexate)** [BZP antagonist]

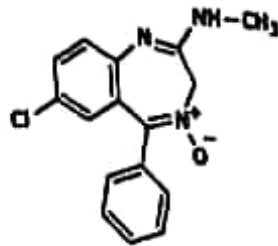


د کانت بنزین

تقر hangover - الحانزید الجریعة

(i) 1,4-Benzodiazepine-4-oxides

Chlordiazepoxide



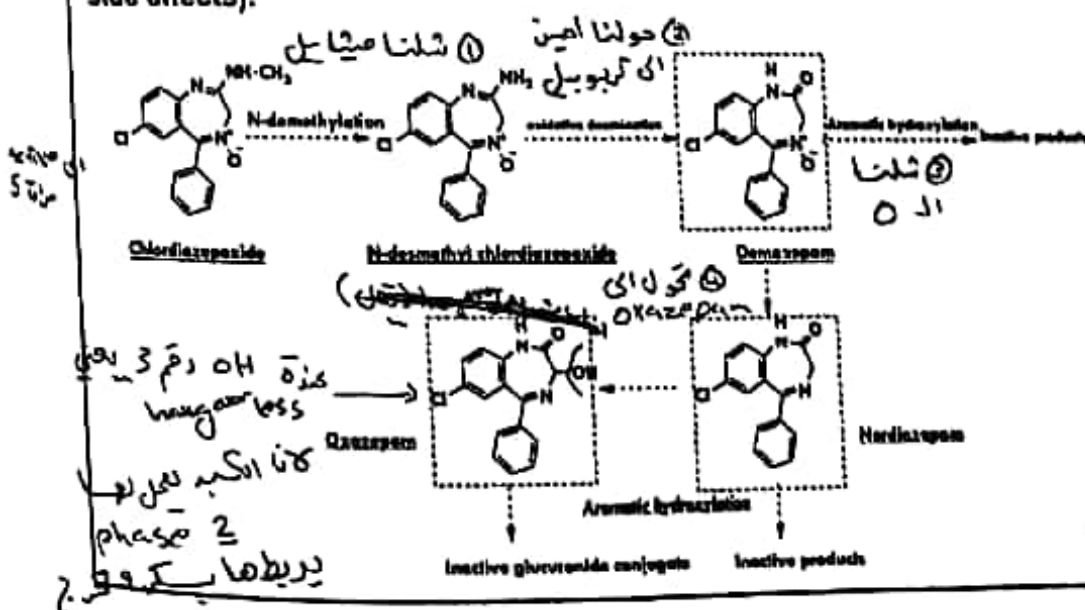
• The **PROTOTYPE**.

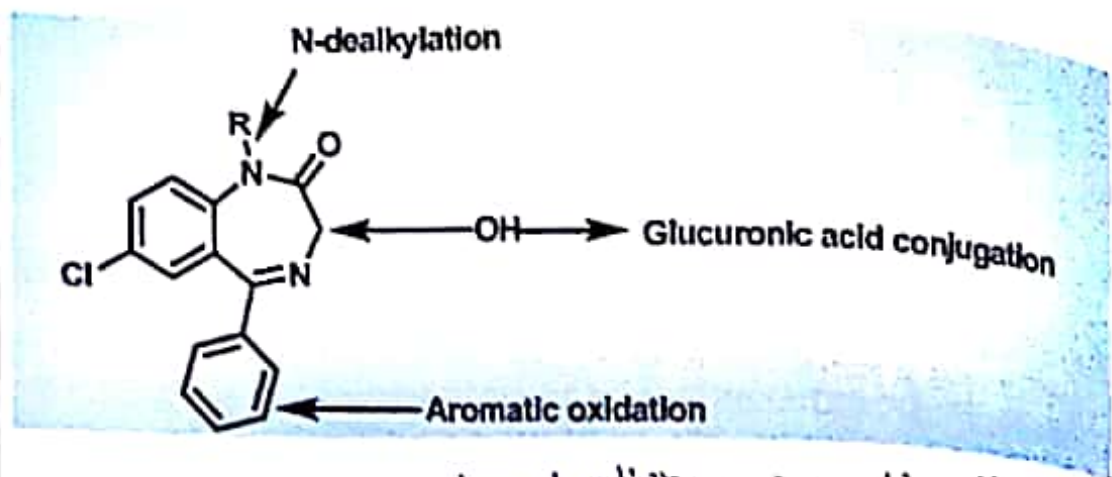
• **Librax®** → drug in market used in spastic colon composed of Chlordiazepoxide + Citidinium bromide [**anti-cholinergic**].

فیاد hangover - یکن کام الدواد سیکول ای active فم مارک

Metabolism of chlordiazepoxide : (active metabolites → available in the market → discovered by **METABOLIC STUDIES**)

The metabolites have less duration and less hanging time (i.e. less side effects).





depression long duration یطی ← lipophilic ای
 short یطی ← hydrophilic ای
 phase 2 ← OH ← لوعلال

Ring A:
 I. Electron withdrawing gp at C₇ is essential (Cl, F, NO₂)
 Position 6,8,9 should not substituted.

Ring System

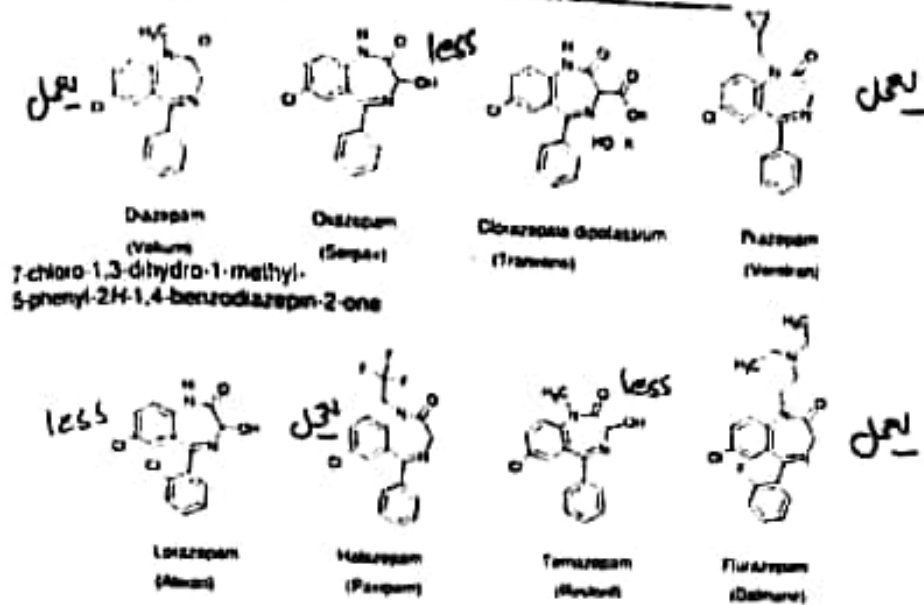
5-Phenyl-1,4-benzodiazepin-2-one

*** Ring C:**
 1. Aromatic (phenyl or isostere "pyridine")

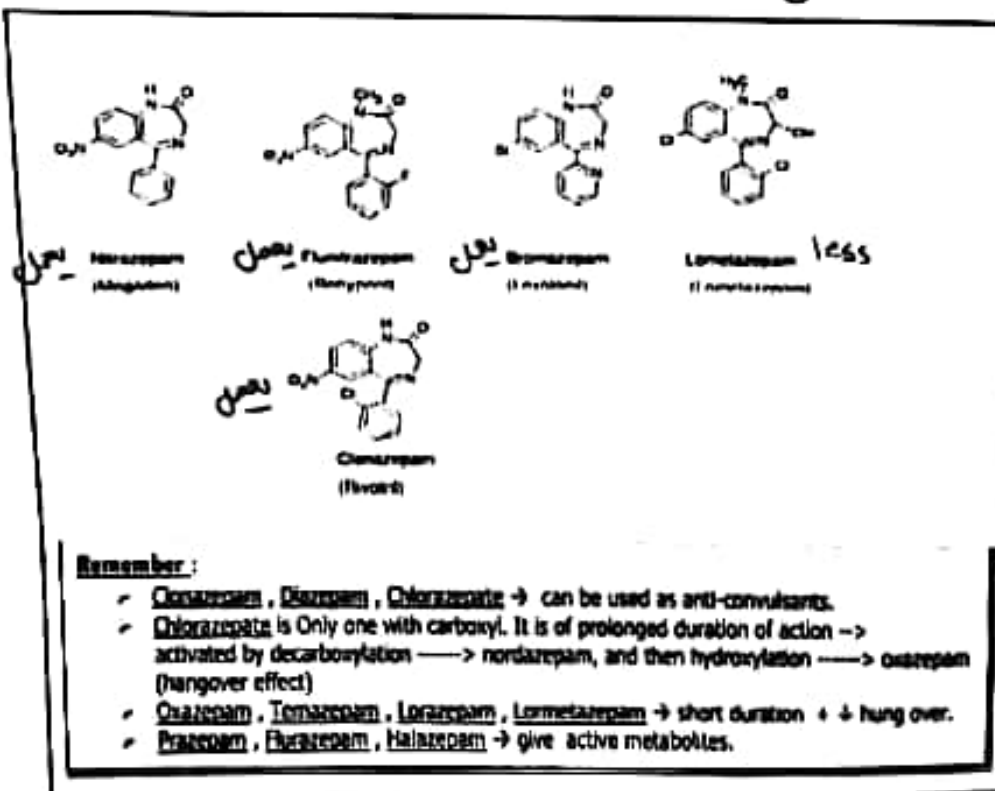
*** Ring B:**
 I. 7-membered imino-lactam ring is essential.
 II. The 2-carbonyl function is for activity [but may be replaced by S].
 III. Position 3 may be unsubstituted or substituted with OH or COOH.
 [OH → ↑ hydrophilicity → ↑ excretion → short duration of action, but ↓ hanging over effect + injectable]

(ii) 1,4-Benzodiazepine-2-ones

This class initiated by metabolic studies.



لما تكافنا الادوية duration طولاً نقص hangover
نستخدمها المصريح



Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation

Anxiety is an unpleasant state of tension, or "a fear that seems to arise from a sometimes unknown source."

Anxiety → Tachycardia, palpitation, تعرق

مقابل Alprazolam و Triazolam و Midazolam (Xanax) — less hangover — CH₃ متاثر ہے
 لیکن یہ الادویہ بھی ادا کرتی ہیں
 فائزہ بھی ہے hangover قتل ideal hypnotic

[iii] 1,2-Annulated-1,4-Benzodiazepine

Alprazolam (Xanax)	Triazolam	Midazolam
		May be used as general anaesthetic

Metabolism: Hydroxylation of the methyl group → glucuronidation → so, they are **SHORT ACTING DRUGS** (may not impair day activities).
 Can be used as **HYPNOTICS** because of short duration. There is **NO HANGING OVER**.

(ideal hypnotic: take before sleep and wake up fine without drowsiness from hanging over effect)

تاکہ سیرج
 سیکو لہ کی طرف
 ہذا، سوایہیں
 نوم مثالی

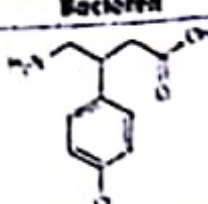
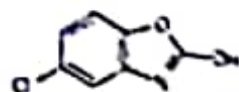
لوہنڈا
 جزیفہ

GABA Amino butyric acid

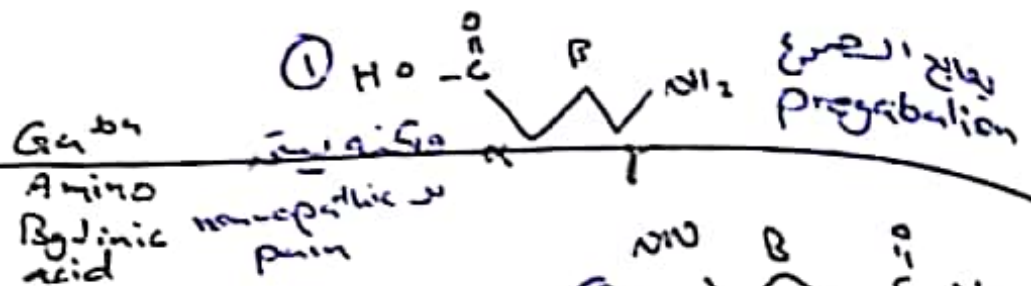
ماده شیمیایی
تداخل با عصب
فرز دنا حلقه
نیزین

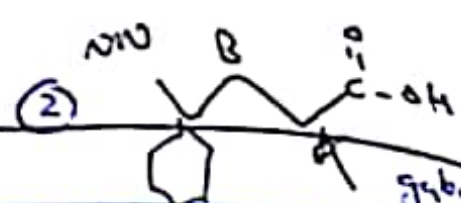
افضل بنیه طبیعی ریشه

Skeletal Muscle Relaxants

Baclofen	Chlorzoxazone
	
GABA derivative, used in spastic diseases of spinal cord	

اینها برای درمان اسپاستیک



② 

③ 

Neuropathic pain

Neuropathic pain

Thank you

بازایج

neuropathic
ریز آلام باکتری
آلام باکتری
من عصبان

آلام عفونی
neuropathic
آلام شایع
در کودکان